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SEVERITY LEVELS AND SYMPTOMS COMPLEXES FOR **ACUTE RADIATION SICKNESS**

Description and Quantification

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Technical Report

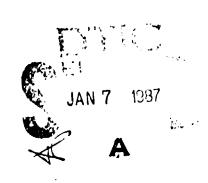
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exposure and injury in humans. Radiation doses in the range of 75 to 4500 rads (cGy) and postexposure times up to 6 weeks are considered. Symptom severity levels, ranging from level					
1 (no apparent effect) to level	l 5 (maximum se	verity), are d	lefined for	each o	f /pix symptom
categories including:(1) upper	gastrointestin	al distress,	(2) lower Ag	gastroi	ntestinal>dis-
tress, (3) fatigability and we	akness, (4) hyp	otension, (5)) infection,	, bleed	ing, and fever,
and (6) fluid loss and electro	lyte imbalance.		ito, b	42	
Temporal profiles of symptom so	everity are devi	eloped for th	•	_	egories as well
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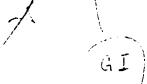
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Postexposure Response Radiation Exposure Radiation Sickness Symptomatology Symptom Complex Symptom Incidence Symptom Sequelae Symptom Severity

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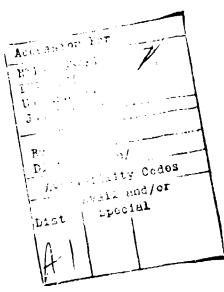
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six integers each ranging from 1 to 5. About 100 different symptom complexes cover the dose and time ranges of interest. A dose/time mapping of the symptom complexes was utilized to select 30 to 40 of the most important ones. Those were included on U.S. Army questionnaires designed to obtain personnel judgments of task performance under various degrees of debilitation. The incidence of upper gostrointestinal distress, lower gastrointestinal distress, fatigability and weakness, and early diarrhea are estimated based on probit and logit analyses of medical data.



GI





SUMMARY

As a first step toward estimating combat troop performance after the detonation of nuclear weapons, Pacific-Sierra Research Corporation (PSR) described typical human symptoms in response to prompt ionizing radiation during the acute period of six weeks after exposure [Baum et al., 1984]. As a second step, this report describes the development and quantification of symptom severity levels and symptom complexes of acute radiation sickness. The effort provides part of the groundwork for designing questionnaires administered to selected U.S. Army personnel. The responses to those questionnaires will be used to judge military task performance by crewmembers suffering from various biological effects of acute ionizing radiation sickness.

Based on a comprehensive review of the symptomatologic sequelae of acute radiation sickness, symptoms were divided into six categories: (1) upper gastrointestinal distress (UG); (2) lower gastrointestinal distress (LG); (3) fatigability and weakness (FW); (4) hypotension (HY); (5) infection, bleeding, and fever (IB); and (6) fluid loss and electrolyte imbalance (FL). For each category, descriptive phrases were developed to denote five different and increasing levels of symptom severity (assigned Nos. 1 through 5) covering the full range of radiation-induced states of illness. That provides a scaling structure to gauge the degree of biological response to injury following radiation exposure.

Graphic profiles were developed to represent symptom severity levels for each of the six symptom categories as functions of postexposure time [ranging from 15 minutes to 6 weeks for eight dose ranges between 75 to 4500 rads (cGy)* free-in-air[†]]. The temporal symptom severity profiles for each of the symptom categories represent the "typical" time-severity response profiles based on the symptomatologic review of the literature. Estimates of the incidence of some selected prodromal symptom categories such as UG (nausea and vomiting),

One centigray (cGy) is equal to one rad.
Unless otherwise stated, all dose levels are free-in-air values.

FW, and LG (diarrhea) as a function of dose are presented in the appendix.

Symptom complexes were formed by combining the temporal profiles of the symptom categories for each dose range. By superimposing the time-dependent symptom severity levels for each of the six symptom categories, symptom complexes were formed. Each complex is represented by a set of six digits ranging from 1 to 5, designating the severity level of each symptom category.

Of the large number of mathematically possible symptom complexes (15,625), only 100 symptom complexes pertain to the dose and time ranges of interest here. Even so, that number proved to be substantially higher than could be included in the U.S. Army questionnaires. Administering the questionnaire was limited by the length of time allotted and by the respondent concentration span. A graphical approach was used to select the symptom complexes for the questionnaire. Approximately 30 to 40 symptom complexes from the most important areas of interest were selected.

PREFACE

This report was prepared by Pacific-Sierra Research Corporation (PSR) as one of a series of reports comprising a portion of the work performed for the Defense Nuclear Agency (DNA) Intermediate Dose Program (IDP) under contract DNA001-84-C-0289. This report describes and quantifies symptom severity levels and the development of symptom complexes to characterize acute radiation sickness resulting from prompt exposure to ionizing radiation in the dose range of 75 to 4500 rads (cGy) free-in-air. The symptom complexes, which designate the state of radiation sickness over a postexposure period of approximately six weeks, provide information for deriving U.S. Army personnel estimates of military task performance levels.

This effort was performed under the guidance and direction of DNA staff members Dr. David Auton and Dr. Robert W. Young, Science and Technology, Biomedical Effects Directorate (STBE).

The authors would like to acknowledge the support provided by members of the IDP core group and in particular, the following individuals who actively participated in developing the symptom severity levels: Dr. H. Rodney Withers, Department of Radiation Oncology, Center for Health Sciences, University of California, Los Angeles; Dr. Robert W. Young and Mr. Sheldon Levin, Armed Forces Radiobiology Research Institute, National Naval Medical Center, Bethesda, Maryland; Dr. Ben B. Morgan, Jr., Organization Research Group, Norfolk, Virginia; MAJ Pete Myers, U.S. Army Nuclear and Chemical Agency, Fort Belvoir, Virginia; Dr. Norm Dalkey, Engineering System Department (Adjunct Professor and Research Psychologist), University of California, Los Angeles; and Drs. Gene McClellan and Harold Brode, PSR. The authors would also like to recognize Mr. Michael Dore of PSR who assisted in developing the appendix describing symptom incidence.

CONVERSION TABLE

Conversion factors for U.S. Customary to metric (SI) units of measurement.

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angstrom	1.000 000 X E -10	meters (m)
atmosphere (normal)	1.013 25 X E +2	kilo pascal (kPa)
bar	1.000 000 X E +2	kilo pascal (kPa)
barn	1.000 000 X E -28	meter ² (m ²)
British thermal unit	1.054 350 X E +3	joule (J)
(thermochemical)		•
calorie (thermochemical)	4.184 000	joule (J)
cal (thermochemical)/cm ²	4.184 000 X E -2	mega joule/m ² (MJ/m ²)
curie	3.700 000 X E +1	giga becquerel (GBq)*
degree (angle)	1.745 329 X E -2	radian (rad)
degree Fahrenheit	$\tau = (t^{\circ}f + 459.67)/1.8$	degree kelvin (K)
electron volt	1.602 19 X E -19	joule (J)
erg	1.000 000 X E -7	joule (J)
erg/second	1.000 000 X E -7	watt (W)
foot	3.048 000 X E -1	meter (m)
foot-pound-force	1.355 818	joule (J)
gallon (U.S. liquid)	3.785 412 X E -3	meter ³ (m ³)
inch	2.540 000 X E -2	meter (m)
jerk	1.000 000 X E +9	joule (J)
joule/kilogram (J/kg) (radiation dose absorbed)	1.000 000	Gray (Gy)**
kilotons	4.183	terajoules
kip (1000 1bf)	4.448 222 X E +3	newton (N)
kip/inch ² (ksi)	6.894 757 X E +3	kilo pascal (kPa)
ktap (KSI)	1.000 000 X E +2	newton-second/m ²
ktap	1.000 000 X E +2	(N-s/m ²)
4	1 000 000 W F (
micron	1.000 000 X E -6	meter (m)
mil	2.540 000 X E -5	meter (m)
mile (international)	1.609 344 X E +3	meter (m)
ounce	2.834 952 X E -2	kilogram (kg)
pound-force (lbf avoirdupois)	4.448 222	newton (N)
pound-force inch	1.129 848 X E -1	newton-meter (N·m)
pound-force/inch_	1.751 268 X E +2	newton/meter (N/m)
pound-force/foot2	4.788 026 X E -2	kilo pascal (kPa)
pound-force/inch ² (psi)	6.894 757	kilo pascal (kPa)
pound-mass (lbm avoirdupois)	4.535 924 X E -1	kilogram (kg)
pound-mass-foot2	4.214 011 X E -2	kilogram-meter ²
(moment of inertia)		(kg·m²)
pound-mass/foot ³	1.601 846 X E +1	kilogram/meter ³
•		(kg/m ³)
rad (radiation dose absorbed)	1.000 000 X E -2	Gray (Gy)**
roentgen	2.579 760 X E -4	coulomb/kilogram
		(C/kg)
shake	1.000 000 X E -8	second (s)
slug	1.459 390 X E +1	kilogram (kg)
torr (mm Hg, 0°C)	1.333 22 X E -1	kilo pascal (kPa)

^{*} The becquerel (Bq) is the SI unit of radioactivity; 1 Bq = 1 event/s. **The Gray (Gy) is the SI unit of absorbed radiation.

TABLE OF CONTENTS

Section		Page
	SUMMARY	iii
	PREFACE	V
	COVERSION TABLE	vi
	LIST OF ILLUSTRATIONS	viii
	LIST OF TABLES	×
1	INTRODUCTION	1
2	SYMPTOM CATEGORY SEVERITY LEVELS	2
3	SYMPTOM CATEGORY SEVERITY PROFILES	6
4	SYMPTOM COMPLEX PROFILES	18
5	SYMPTOM COMPLEX MAPPING	29
6	LIST OF REFERENCES	54
Append	ix	
	INCIDENCE OF SYMPTOMS	. 57

LIST OF ILLUSTRATIONS

Figure		Page
1	Typical time-severity response profile	7
2	UC severity levels for dose ranges free-in-air	8
3	LC severity levels for dose ranges free-in-air	9
14	FW severity levels for dose ranges free-in-air	10
5	HY severity levels for dose ranges free-in-air	11
6	IB severity levels for dose ranges free-in-air	12
7	FL severity levels for dose ranges free-in air	13
8	Symptom severity level profiles for 75 to 150 rads (cGy) free-in-air	19
9	Symptom severity level profiles for 150 to 300 rads (cGy) free-in-air	20
10	Symptom severity level profiles for 300 to 530 rads (cGy) free-in-air	21
11	Symptom severity level profiles for 530 to 830 rads (cGy) free-in-air	22
12	Symptom severity level profiles for 830 to 1100 rads (cGy) free-in-air	23
13	Symptom severity level profiles for 1100 to 1500 rads (cCy) free-in-air	24
14	Symptom severity level profiles for 1500 to 3000 rads (cGy) free-in-air	25
15	Symptom severity level profiles for 3000 to 4500 rads (cGy) free-in-air	26
16	UG symptom severity	37
17	LG symptom severity	38
18	FW symptom severity	39
19	HY symptom severity	40

LIST OF ILLUSTRATIO'S (Concluded)

Figur	'e	Page
20	1B symptom severity	41
21	FL symptom severity	42
22	Six-dimensional map of symptom severity contours	43
23	Construction of symptom complex zone	45
24	Symptom complex zones	46
25	Excluded symptom complex zones	47
26	Early LG symptom complex zones	48
27	Symptom complexes presented on questionnaire	49
28	Incidence of UG	58
29	Incidence of FW	59
30	Incidence of LG	61
31	Incidence of prodromal symptoms	63
32	Incidence of prodromal symptomslognermal and logistic relationships	67

LIST OF TABLES

Tabl	e	Page
1	Radiation sickness symptoms and severity levels by category	4
2	Occurrence of symptoms in complexes	30
3	Onset and duration of symptom complexes	32
4	Prodromal symptom incidence relationship parameters	66

SECTION 1 INTRODUCTION

This report describes the formation of sign/symptom time profiles and symptom complexes of acute radiation sickness through a comprehensive review and assessment of the acute radiation symptomatology in humans [Baum et al., 1984]. The symptom complexes, which are used in U.S. Army questionnaires to obtain estimates of military crewmember task performance, relate performance to dose level and time after prompt radiation exposure [Glickman et al., 1984].

In developing the symptom complexes, the acute radiation symptoms were characterized into six separate categories. Descriptive phrases for each category were developed to distinguish between five different levels of increasing severity covering the full range of possible radiation-induced illness. Using those symptom severity levels, graphical profiles were developed to represent the levels for each of the six symptom categories as functions of postexposure time [ranging from 15 minutes to 6 weeks for each of eight dose ranges between 75 to 4500 rads (cGy) free-in-air [Baum et al., 1984].

of the large number of symptom complexes that are mathematically possible (15,625) only about 100 are necessary to cover the dose and time ranges. Even so, that number is substantially more than can be included in a questionnaire [Glickman et al., 1984]. The administering of the U.S. Army questionnaire is limited by time and by an attempt to preserve the quality of responses (i.e., concentration span of the respondents). Using a graphical approach, we located symptom complexes in the dose/time plane to use as a selection guide. A manageable number of symptom complexes were seler—1 for the questionnaire to achieve fairly complete coverage of the most important areas and of the other areas adequate to interpolate and extrapolate trends.

[&]quot;Throughout this report, "symptom" refers to both subjective and objective signs of radiation sickness.

Unless otherwise stated, all dose levels are free-in-air values.

One centigray (cGy) is equal to one rad.

SECTION 2 SYMPTOM CATEGORY SEVERITY LEVELS

This section describes the approach to gauging the course of acute radiation sickness. Descriptive phrases are used to designate severity level scaling of symptom categories. The scaling structure is necessary to construct time profiles of symptom severity based on the symptomatologic review by Baum et al. [1984].

A standard scale indicating the severity of radiation sickness symptoms does not exist in the literature. Most often, common clinical terms such as "mild," "moderate," or "severe" are used to describe the degree of severity. Specific phrases were developed that describe symptom severity levels in order to establish a common ground for assessing the impact of those symptoms on performance. Personnel who have experienced symptoms of various common illnesses may perceive similar responses, even if they are induced by ionizing radiation. Thus, when radiation sickness levels of severity are accurately described to troop personnel in relation to the performance of specific assigned combat tasks, a judgmental assessment of the ability to perform such tasks can be obtained.

Because the PSR effort includes the combined judgment and consensus of individuals with backgrounds in the fields of radiotherapy, radiobiology, psychology, and small crew military operations, a representative group from all those fields was formed to designate symptom severity levels. First, the group chose six symptom categories based on the symptomatology given by Baum et al. [1984] to describe acute radiation sickness:

- 1. upper gastrointestinal distress (UG),
- 2. lower gastrointestinal distress (LG),
- 3. fatigability and weakness (FW),
- 4. hypotension (HY),

- 5. infection, bleeding, and fever (IB),
- 6. fluid loss and electrolyte imbalance (FL).

Those six categories were chosen because they are (1) generally found in the literature of acute radiation symptomatology; (2) partially separable in terms of dose and time; and (3) reasonably amenable to descriptive phrasing aimed at distinguishing levels of severity within each symptom category.

The group rejected the use of existing sickness scales, such as the Karnofsky scale [Beahrs and Myers, 1983], because they are not specific to the six acute radiation symptom categories. Additionally, they contain words that are performance synonyms, phrased in a manner that assumes the subject is a medical patient. Also, some sickness scales contain too many levels (10 in the Karnofsky scale) for the purposes of this effort. Accordingly, the group elected to use a five-level ordinal scale—each number corresponding to a brief descriptive phrase indicating severity level. The phrases for each symptom category are category—specific, and the numbers represent a hierarchical degree of severity. Table 1 lists the symptom severity levels developed by the group.

Five levels of severity are indicated for each symptom category-level 1 represents no effect and levels 2 through 5 indicate increasing symptom severity. The descriptions of each severity level are brief, concise, and comprehensive so that they can be easily incorporated into the crewmember performance questionnaire. Although each severity level represents a distinct response to radiation injury related to a given dose range, it should be understood that as the radiation dose increases, a specific severity level may change in gradual, moderate steps, rather than abruptly from one severity level to another.

Numbering the severity levels from 1 through 5 anchors the upper and lower limits of severity for each symptom category and implies a linear progression; however, there is no present means of positively determining that. Furthermore, with the exception of severity level 1

Table 1. Radiation sickness symptoms and severity levels by category.

Severity Level	Radiation Sickness Symptom
	UG
1	No effect
2	Upset stomach; clammy and sweaty; mouth waters and swallows frequently
3	Nauseated; considerable sweating; swallows frequently to avoid vomiting
4	Vomited once or twice; nauseated and may vomit again
5	Vomited several times including the dry heaves; severely nauseated and will soon vomit again
	LG
1	No effect
2	Feels uncomfortable urge to defecate
3	Occasional diarrhea, recently defecated and may again
4	Frequent diarrhea and cramps, defecated several times and will again soon
5	Uncontrollable diarrhea and painful cramps
	FW
1	No effect
2	Somewhat tired with mild weakness
3	Tired, with moderate weakness
4	Very tired and weak
5	Exhausted with almost no strength
	нұ
1	No effect
2	Slightly light-headed
3	Unsteady upon standing quickly
4	Faints upon standing quickly
5	In shock; breathes rapidly and shallowly, motionless, skin cold, clammy, and very pale.
	IB
1	No effect
2	Mild fever and headache, as if coming down with flu
3	Joints ache, considerable sweating; moderate fever; no appetite; sores in mouth and throat
4	Shakes, chilis, and aches all over; difficulty in stopping any bleeding
5	Delirious, overwhelming infections; cannot stop any bleeding
	FL
1	No effect
2	Thirsty and has dry mouth; weak and faint
3	Very dry mouth and throat, headache; rapid heartbeat and may faint with moderate exertion
4	Extremely dry mouth, throat, and skin and very painful headache; has
5	difficulty moving; short of breath; burning skin and eyes Prostrate

and to a lesser extent level 5, there is not any particular quantitative equivalence of severity levels across symptom categories.

It should also be noted that while we have attempted to avoid direct reference to any degree of performance, we realize that level 5 descriptions for HY--containing the word "shock;" FL--containing the word "prostrate;" and IB--containing the word "delerious," denote incapacitation.

The structure and wording of the symptom descriptions resulted from an iterative refinement process involving several steps, including advice from radiobiologists and the pilot testing of the questionnaire using representative U.S. Army personnel. The group applied the following set of guidelines to the structuring process.

- Impart an effective perception of the symptoms of acute radiation sickness.
- Clearly delineate levels of severity within the symptoms.
- Limit the number of severity levels to be consistent with the level of detail appearing in the literature.
- Avoid the repeated use of leading adjectives such as mild, moderate, or severe.

SECTION 3 SYMPTOM CATEGORY SEVERITY PROFILES

The acute radiation severity levels defined for the symptom categories discussed in Sec. 2 provide the scale structure to develop severity profiles for each symptom category over time, following radiation exposure. In this section, we describe how descriptions reported by Baum et al. [1984] have been expanded to specifically detail the course of acute symptomatology over time.

In the typical symptom description given by Baum et al. [1984], there is no attempt to detail the time-varying degree of severity because of the lack of specific time-resolved data. However, for tactical planning, it is important to predict whether or not military personnel will be able to perform specific battlefield tasks and for what length of time after nuclear radiation exposure. Accordingly, temporal occurrence of radiation sickness symptoms must be linked wit the distribution of their severity. The literature does not provide enough specific quantitative evidence on acute radiation sickness symptomatology to readily support the development of detailed timeseverity response profiles. The literature does, however, offer general and spotty guidance for constructing such symptom severity profiles for the "typical person" depicted by Gerstner [1958a,b, 1960] (see Fig. 1); Laumets [1965], Lushbaugh [1967, 1969, 1973]; Brown and Doll [1957]; Hubner and Frye [1980]; Withers [1982]; Messerschmidt [1979]; International Atomic Energy Agency and World Health Organization [1961]; and Brucer [1959]. Using those sources together with more specific pathophysiological information from Baum et al. [1984] the symptom severity profiles were constructed.

The appendix provides a means of estimating symptom incidence as a function of dose level. However, as pointed out by Baum et al. [1984], the incidence of symptoms based on probit analyses

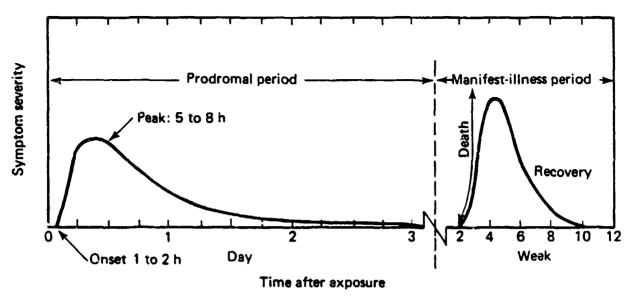


Figure 1. Typical time-severity response profile for dose range 200 to 600 rads (cGy).

of data of Japanese atomic bombing survivors, nuclear accident victims, and radiation therapy patients are also not specifically correlated with postexposure time. But because the typical postexposure time-course of symptoms is well known, incience/time correlations for symptom categories such as UG, FW, and early can be infered; at least the prodromal period. The incidence regarding other symptom categories such as HY, FL, and IB are given by Baum et al. [1984].

For the six symptom categories, profiles were developed by plotting severity level against time from 15 m² to 6 weeks after exposure to radiation in eight separate dose ranges: 75 to 150 rads, 150 to 300 rads, 300 to 530 rads, 530 to 830 rads, 830 to 1100 rads, 1100 to 1500 rads, 1500 to 3000 rads, and 3000 to 4500 rads (cGy). Those plots, shown in Figs. 2 through 7 indicate the severity levels for the six symptom categories during acute radiation sickness for a typical individual after exposure.

The severity profiles are represented by a collection of straight-line segments forming families of curves for each symptom category. The lack of both the amount and accuracy of severity-time response data for acute radiation syndrome does not permit detailed

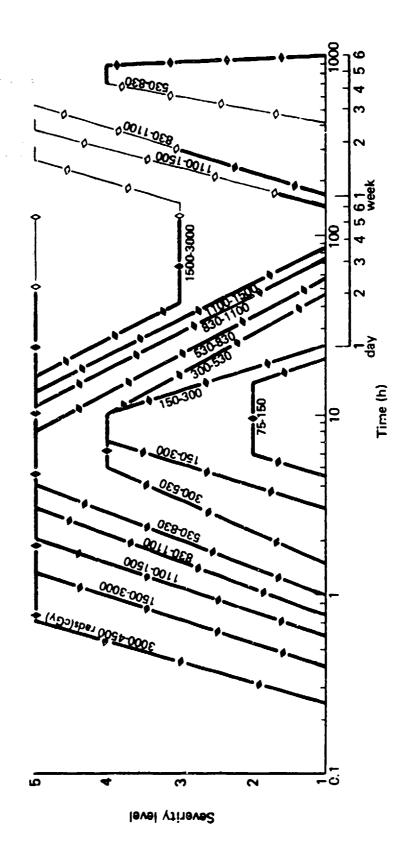


Figure 2. UG severity levels for dose ranges free-in-air.

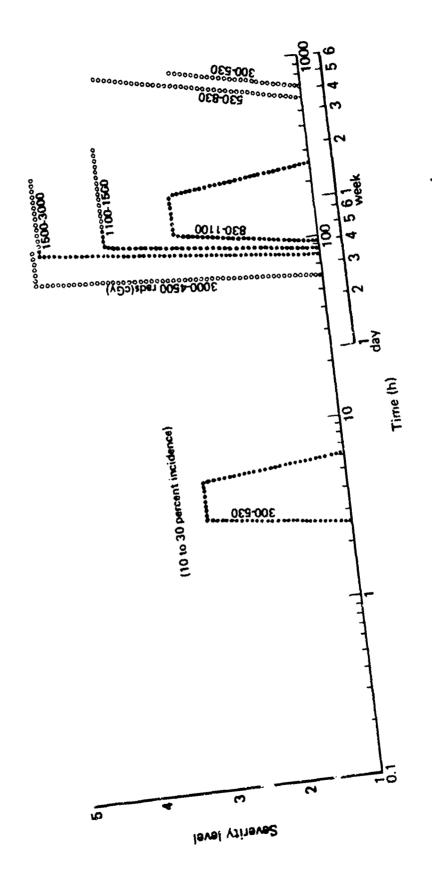


Figure 3. LG severity levels for dose ranges free-in-air.

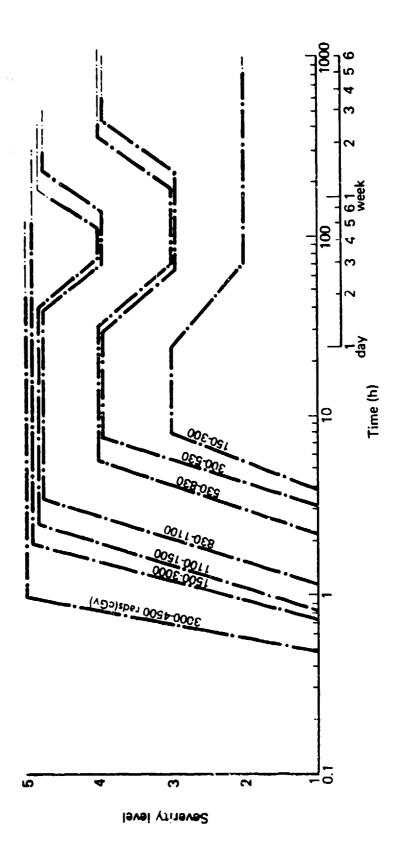


Figure 4. FW severity levels for dose ranges free-in-air.

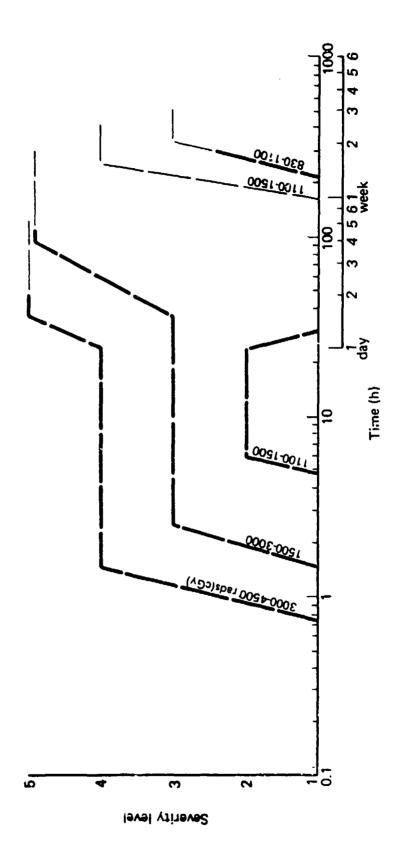


Figure 5. HY severity levels for dose ranges free-in-air.

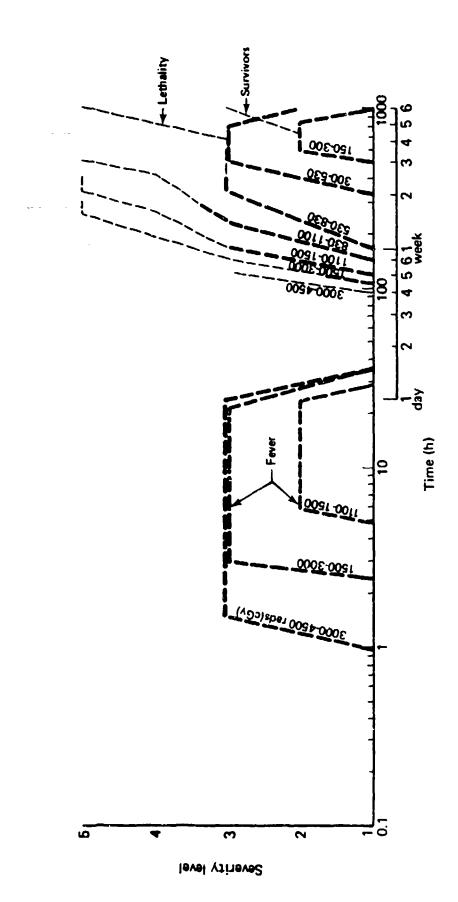
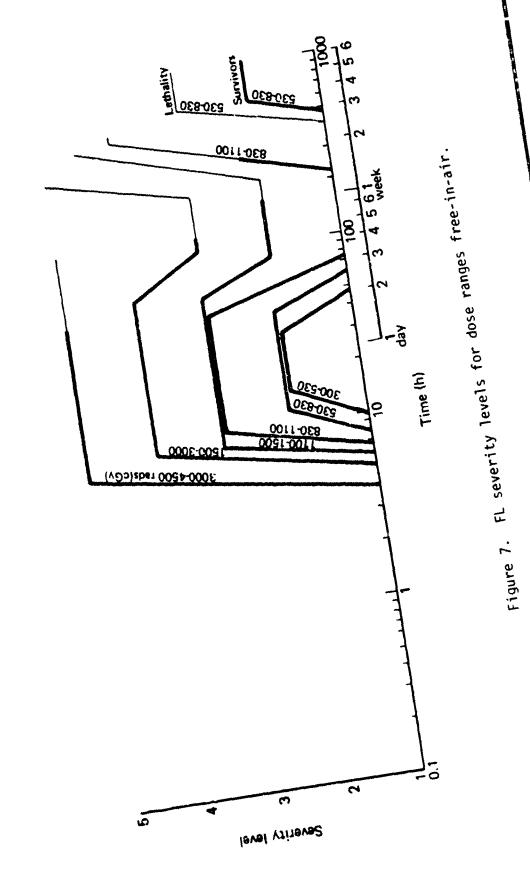


Figure 6. IB severity levels for dose ranges free-in-air.



functional modeling of the dose-time response for acute radiation symptomatology. However, review of the literature by Baum et al. [1984] and other sources indicates that the profile given in Fig. 1 is a reasonable representation of the time-course of acute radiation sickness symptomatology. Also, for doses greater than the range shown in Fig. 1 [about 200 to 600 rads (cGy)], there is a progressively steeper symptom severity level rise time, as well as a prolonged lengthening of those symptoms after reaching maximum fulmination. For example, Lushbaugh [1969] points out that after a few thousand rads of prompt whole-body radiation exposure, prodromal symptoms are expected to begin within 5 to 15 min, reach full intensity in about 30 min, and persist for several days, gradually diminishing until merging with the universally fatal vascular syndrome or with the fatal dysenteric syndrome after doses of 1000 rads (cGy). Also, there is a later onset, increasing rise time, and a shorter recovery period after decreasing radiation exposure levels. Those concepts were used in constructing the severity profiles shown in Figs. 2 through 7.

The abscissa (time axis) in Figs. 2 through 7 is represented logarithmically; however, the straight lines indicating the rise and fall of severity would resemble the kind of profile shown in Fig. 1 if plotted along a linear time axis (excluding the flat peaks, of course). Also, symptom remission does not occur at higher dose levels particularly in the FW, HY, and to a certain extent FL symptom categories. The lightly drawn curves represent the time span in which lethalities occur [Baum et al., 1984].

based on the review of ionizing radiation effects in humans by Baum et al. [1984], moderate UG occurs during the first day after exposures from 300 to 530 rads (cGy)--nausea is accompanied by a few episodes of vomiting. Accordingly, severity level 4 in the UG category (see Table 1) lasts from 5 to 10 h postirradiation, subsides to severity level 3, and finally to severity level 2 by the end of the first day.

The FW symptoms (Fig. 4) appear early after radiation exposure-within hours--even at lower doses, and approach severity level 4 after doses exceed 300 rads (cGy) and level 5 after doses exceed 830 rads (cGy). For the dose range 150 to 350 rads (cGy), Baum et al. [1984] characterize the FW category as mild to moderate for the first day or two which matches both descriptions given for FW severity levels 2 and 3 in Table 1. However, in order to avoid noninteger severity level assignment, we took a conservative approach and designated FW severity level 3 over a period of 8 to 24 h for that dose range. Similarly, for the next higher dose range of 300 to 530 rads (cGy), Baum et al. [1984] characterize the FW category as moderate for the first day or two which matches the description given for FW severity level 3. However, after a subsequent review of the literature on fatigability symptoms of acute radiation sickness [Gerstner, 1958,a,b, 1960; Lushbaugh et al. 1969, 1973; Brown, Court, and Doll, 1957; Hubner and Fry, 1980; Messerschmidt, 1979; Robin and Cassarett, 1968; Ricks et al., 1972; Hall, 1978], FW symptoms are more severe for that dose range, somewhere between the descriptions given for FW severity levels 3 and 4. Again, the conservative approach was used which shows FW severity level 4 present approximately 8 to 30 h in dose ranges 300 to 530 rads (cGy). That level declines to level 3 by the end of the first day (Fig. 4). Figure 6 shows that the IB category reaches severity level 3 only from three to five weeks postirradiation for that dose range. Although only a moderate effect, that degree of infection may cause 50 percent fatalities as the dose reaches 530 rads (cGy).

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Not surprisingly, Figs. 2 through 7 indicate increasing levels of radiation sickness severity and increasing duration as the dose of ionizing radiation increases. The UG symptoms (Fig. 2) are temporary and may not decrease functional capacities beyond the first day or so at doses from 150 to 530 rads (cGy). Beyond that dose range, particularly as the dose approaches 830 rads (cGy), acute radiation effects become manifestations of the gastrointestinal syndrome. The LG symptoms (Fig. 3) may only be observed in subjects occasionally (approximately 10 percent) prior to the third day postirradiation

[Withers, 1982]. The effects of LG damage play an important role in the final phases of the hematopoietic and gastrointestinal radiation syndromes as the dose increases.

The symptoms of HY (Fig. 5) are primarily observed at radiation doses above 1000 rads (cGy) [in the dose range from 1500 to 3000 rads (cGy)], Severity levels 4 and 5 are part of the terminal phase of radiation sickness [Prasad, 1974]. Injury to radiosensitive organs probably induces the fever associated with severity levels 2 and 3 after exposures of 1100 rads (cGy) during the first 24 to 36 h (Fig. 6). That fever is not the result of septicemia. Although depression of granulocytes and platelets is observed at exposures below 300 rads (cGy), spontaneous recovery is usually complete. Exposed personnel may bruise easily between the third and sixth week postirradiation. At doses from 300 to 800 rads (cGy), granulocytes and platelets are severely depleted. That usually results in fever and bleeding as described in severity level 3 in the IB category and (Table 1), and occurs between two and six weeks postirradiation. The IB symptoms may be severe enough at approximately 300 rads (cGy) to cause lethalities; the LD50 dose is at approximately 450 to 490 rads (cGy).

Beyond 800 rads (cGy), IB is described in terms of severity levels 4 and 5 (see Table 1) between two to three weeks postirradiation. Near 100 percent fatalities are predicted in untreated personnel. Severity levels 4 and 5 for IB are observed between one and two weeks after irradiation from doses of 1200 to 3000 rads (cGy). The pathological effects of gastrointestinal damage increase rapidly with increasing radiation dose. Infection is caused by unchallenged bacteria escaping from the gut, since granulocytes are no longer produced in the bone marrow.

Beyond 3000 rads (cGy) death is caused within two to five days due to severe fluid and electrolyte losses from the vascular system and intestinal tract compounded by cardiovascular impairments. The FL (Fig. 7) during the first day after radiation is primarily caused by

The lethal dose occurring in 50 percent of those exposed, within 60 days.

vomiting and reaches severity level 2. That level results from radiation exposures up to 830 rads (cGy), level 3 up to 1100 rads (cGy), level 4 up to 3000 rads (cGy), and level 5 beyond that.

Irradiation of 3000 rads (cGy) and above (which causes death within two to five days) may well cause prostration as described by severity level 5 by the end of the first day. Personnel subjected to radiation doses below 1000 rads (cGy) usually recover from the initial fluid imbalance caused by emesis during the first 24 to 48 h; however, severity levels 3 to 4 in the FL category may further aggravate the terminal infecticus phase prior to death between 3 to 6 weeks.

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SECTION 4 SYMPTOM COMPLEX PROFILES

In this section symptom complex time profiles are described for the eight dose ranges discussed previously. The profiles are formed by superimposing the individual symptom categories for each dose range along the postexposure time axis. They illustrate the symptom temporal sequelae for acute radiation sickness and provide the basis for the selection of the symptom complexes described in Sec. 5.

Each individual who may be exposed to prompt ionizing radiation may not exhibit all the symptom response categories in the manner outlined by the symptom complex profiles. However, based on the review and analysis of Baum et al. [1984], we are satisfied that the typical response is represented in the profiles illustrated in Figs. 8 through 15.

Figures 8 through 15 represent the severity levels of the six symptom categories plotted against the logarithm of postexposure time, respectively, for the eight dose ranges [75 to 150, 150 to 300, 300 to 530, 530 to 830, 830 to 1100, 1100 to 1500, 1500 to 3000 and 3000 to 4500 rads (cGy) free-in-air]. Figure 8 reveals that for the dose range of 75 to 150 rads (cGy), only the UG category shows mild effects as expressed by severity level 2 between 6 to 16 h postirradiation. All other symptom categories are not included. At the next higher dose range (see Fig. 9), 150 to 300 rads (cGy), the categories UG and FW show elevation to severity levels 4 and 3, respectively, during the prodromal period. Four to six weeks later, the FW category is still at severity level 2; and at that time IB is also at severity level 2. Approaching 300 rads (cGy), the severity level of IB may reach level 3 in approximately 2 to 5 percent of exposed personnel who represent the percentage of nonsurvivors [Prasad, 1974; Bond, Fliedner, and Cronkite, 1960].

Although the severity levels were derived independently for each symptom category, severity levels of some symptom categories may have

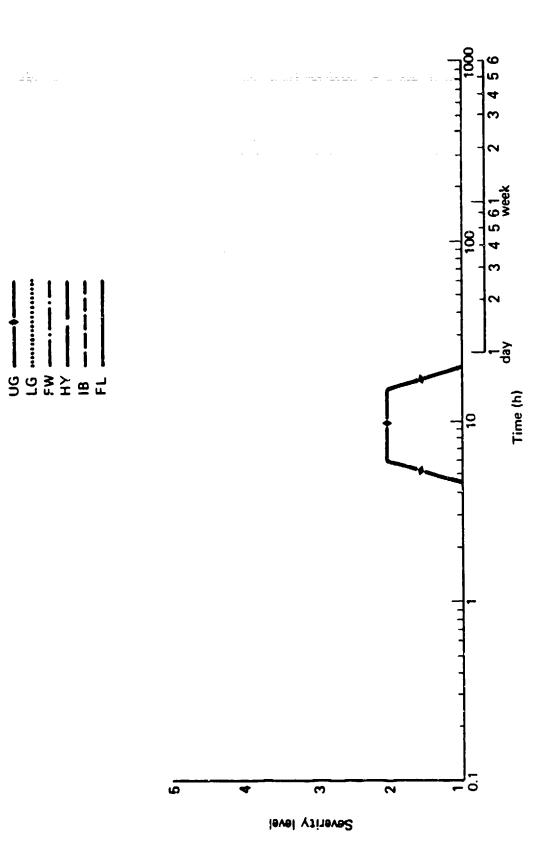


Figure 8. Symptom severity level profiles for 75 to 150 rads (cGy) free-in-air.

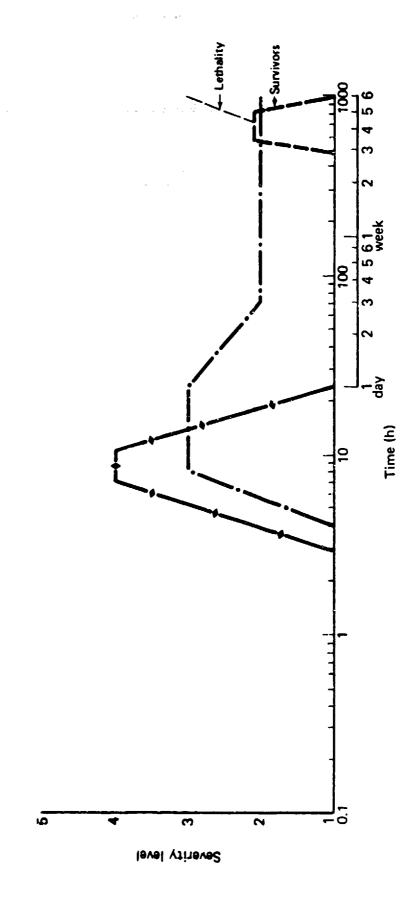


Figure 9. Symptom severity level profiles for 150 to 300 rads (cGy) free-in-air.

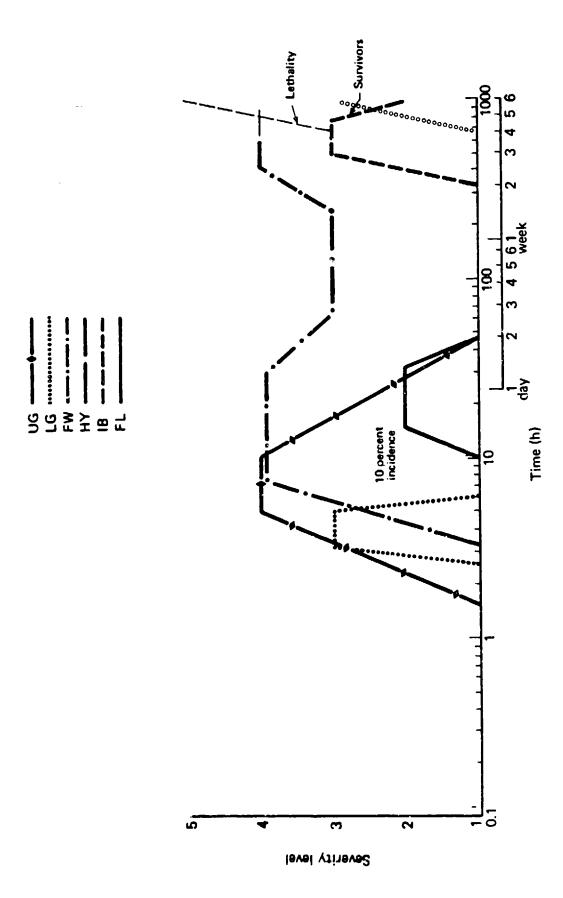
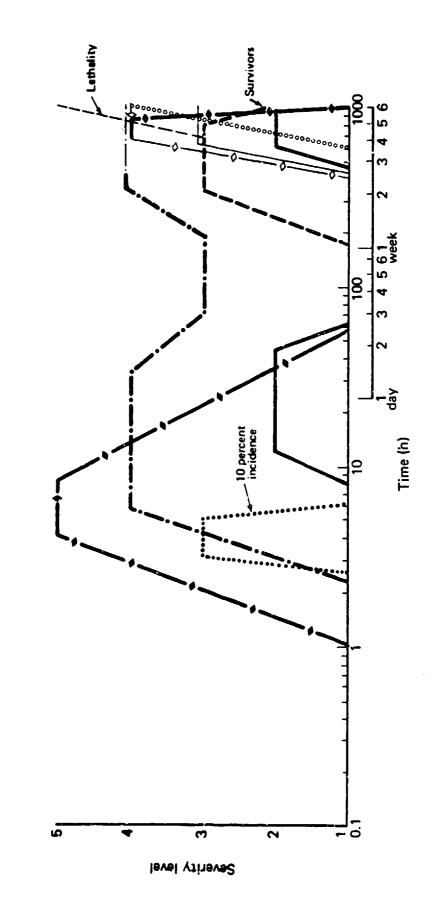
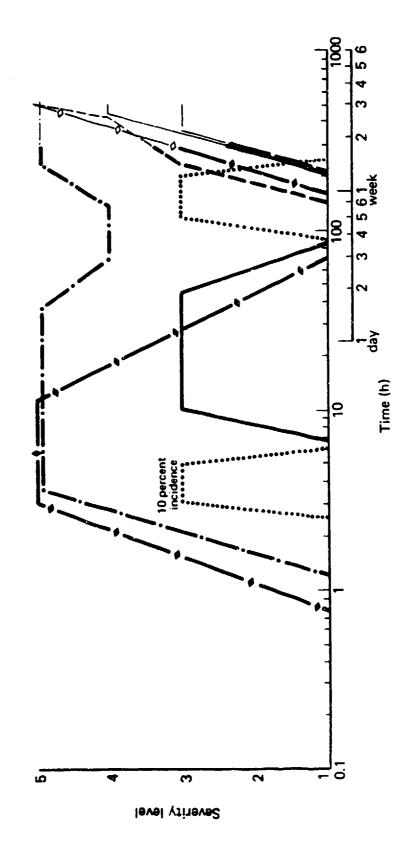


Figure 10. Symptom severity level profiles for 300 to 530 rads (cGy) free-in-air.



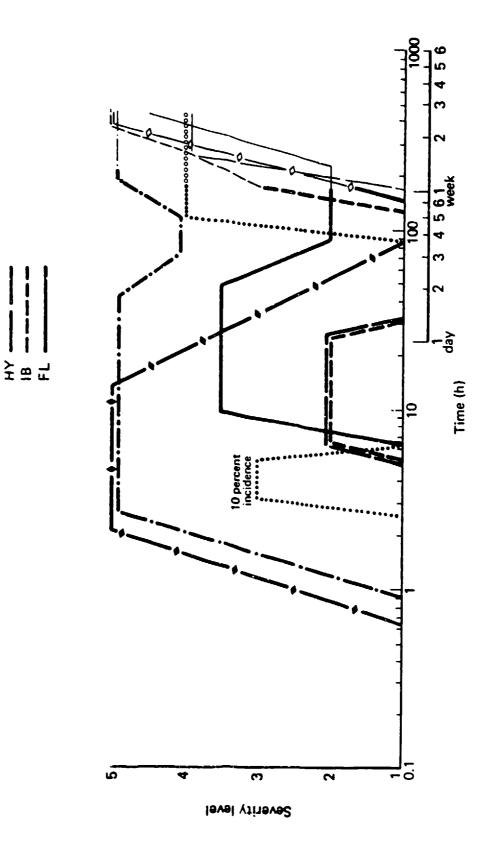
UG LG F¥ H BH F

Figure 11. Symptom severity level profiles for 530 to 830 rads (cGy) free-in-air.



Symptom severity level profiles for 830 to 1100 rads (cGy) free-in-air. Figure 12.

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UG LG FW

Figure 13. Symptom severity level profiles for 1100 to 1500 rads (cGy) free-in-air.

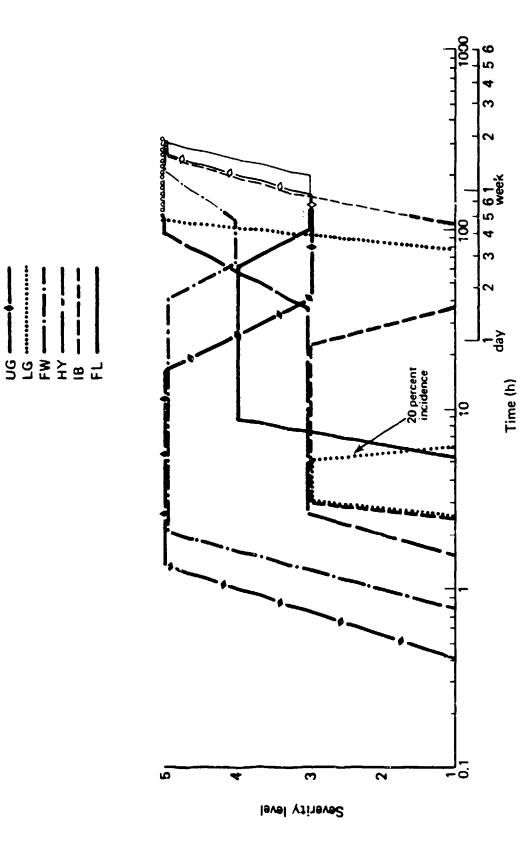
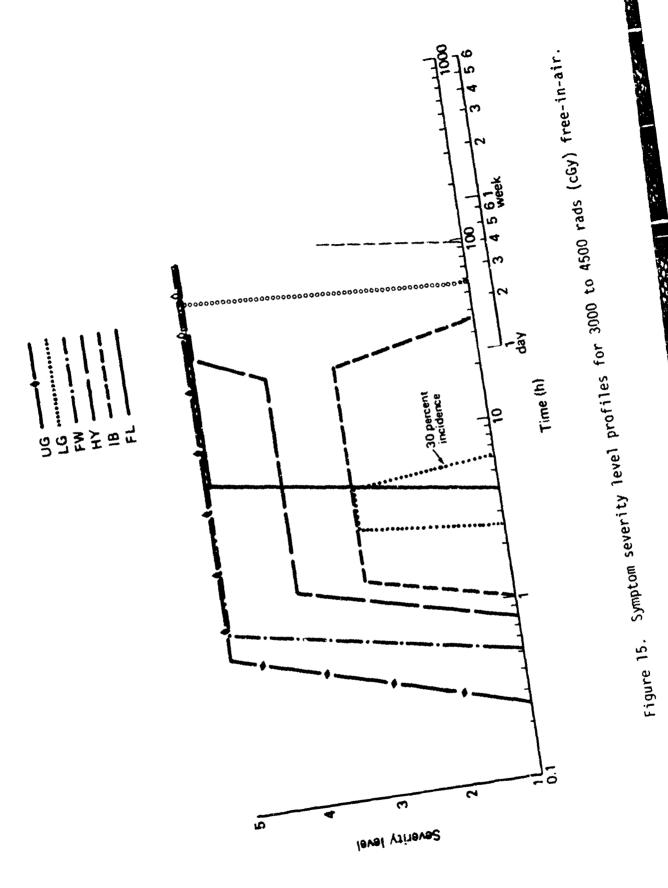


Figure 14. Symptom severity level profiles for 1500 to 3000 rads (cGy) free-in-air.



similar pathophysiological effects. For example, during the prodromal period between about 12 to 16 h, the severity level in the categories of UG and FW is 3 (Fig. 9). At that time, the exposed individual may have just completed vomiting episodes and is still very nauseated. He is also tired with moderate weakness and has reduced strength. Pathophysiologically, his condition could be explained in various ways. Most likely, the FW symptoms were induced by the previous periods of vomiting and nausea. That would indicate that the observed effects are primarily of UG origin. Although, when the UG symptoms completely subside, continuing FW effects could be due to radiation-induced changes in the biochemical pathways of the neuromuscular system. Whether or not there is a cause and effect relationship between UG and FW symptom categories, the initial debilitating effects present in the prodromal phase are due primarily to UG distress which reaches severity level 4. Any lingering, but reduced debilitating is due to FW. Between four to six weeks, any debilitation effects may well be caused by IB rather than FW [Ohkita, 1975].

It is not clear to what degree a second symptom category of equal or lesser severity level may increase radiation illness caused by any one category alone. Consequently, in Figs. 10 through 15, as the radiation doses increase and the severity levels of all categories rise, extreme care must be taken in evaluating the condition before compounding possible effects. Indeed, in a number of instances, one or at most two categories may be primarily responsible for the underlying pathophysiology and possible impaired functional performance capability of an individual.

The effects in the dose range of 300 to 530 rads (cGy) (Fig. 10) are similar to those in the previous range (Fig. 9); however, as severity levels increase with dose, the question of the origin and contribution of the FW symptoms may be raised again during the prodromal period, and even 3 to 6 weeks later during the hematopoietic period. Figure 10 also indicates survival and nonsurvival severity levels. That is, when IB severity level 3 is reached at 3 to 4 weeks postexposure, from 2 to 5 percent up to 50 percent

lethality would be expected to result from the effects of hematopoietic injury.

The radiation dose range of 530 to 830 rads (cGy) (Fig. 11) shows that effects of UG and FW severity levels 5 and 4, respectively, are primarily responsible for the prodromal manifestations. In a few percent the LG effects may be present prior to 6 h and excessive vomiting may induce mild FL symptoms between 12 and 36 h. Between four to six weeks, severe bone marrow destruction causes the hematopoietic radiation syndrome resulting in 50 to 100 percent fatalities in exposed personnel. The FW 3 and 4 severity levels preclude any demanding activities between the second day when the prodromal effects subside and three to four weeks later when the hematopoietic symptoms appear.

Effects become more severe with increasing dose ranges (Figs. 12 through 14) resulting in earlier incapacitation and death [Baum et al., 1984]. Damage to the gastrointestinal system becomes predominant at the dose range of 1500 to 3000 rads (cGy) (Fig. 14) and eventually exposed persons die from severe infections, fluid loss, and shock. At that dose range, deleterious contributions from all symptom categories may be observed. Finally, at the dose range from 3000 to 4500 rads (cGy) (Fig. 15), the UG, FW, and HY effects induce severe debilitation during the first 48 h. Those symptoms can persist until death approximately two to five days later, caused from fluid loss and electrolyte imbalance terminating in irreversible shock due to extreme damage to the gastrointestinal and cardiovascular system.

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SECTION 5 SYMPTOM COMPLEX MAPPING

Specific symptoms occur in individuals exposed to acute doses of radiation ranging from 75 to 4500 rads (cGy). Symptoms that occur at the same time are grouped as symptom complexes to describe sickness states. The complexes are identified by a six-digit code number, for example, 214 112. Each digit in that code corresponds to one of the six symptoms listed in Table 1. The value of each digit indicates symptom severity, ranging from 1--no effect to 5--maximum effect. The code number 214 112 indicates: no effect for the second (LG), fourth (HY), and fifth (IB) symptom category; severity level 2 for the first (UG) symptom category; severity level 4 for the third (FW) symptom category; and severity level 2 for the sixth (FL) symptom category.

Over 100 symptom complexes can occur for doses between 75 and 4500 rads (see Table 2). U.S. Army personnel were asked about the effects of relatively few symptom complexes due to questionnaire limitations. A method was devised by which a cross section of the complexes were selected for the questionnaire [Glickman et al., 1984]. In order to assess the relative importance of symptom complexes the following were considered:

- frequency of occurrence of particular severity levels across symptom categories,
- early and late occurrence,

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- brief and protracted occurrence,
- low and high dose occurrence.
- 5. continuity of occurrence in both dose and time.

Although the above can be numerically tabulated (see Table 3), a non-numerical method is necessary to complete a comprehensive assessment of the symptom complexes. A topological approach was taken by mapping the symptoms on the time-dose plane-representing the six symptom

Table 2. Occurence of symptoms in complexes.

Symptom Category	Level	Occurrences in Likely Symptom Complexes	Occurrences in Less Likely Symptom Complexes		rences tionnaire TOW Crews
UG	1 2 3 4 5	19 10 23 20 36	19 10 19 16 22	5 3 8 6 8	6 3 1 0
LG	1 2 3 4 5	66 7 15 10 9	60 6 11 8 0	24 4 2 0 0	10 0 0 0 0
FW	1 2 3 4 5	3 5 7 35 53	3 5 7 30 38	4 3 8 8 7	2 3 1 4 0
нұ	1 2 3 4 5	55 9 14 14 15	54 7 12 10 0	25 2 2 1 0	10 0 0 0
IB	1 2 3 4 5	51 18 23 8 7	47 13 19 8 0	26 2 2 0 0	5 2 3 0 0
FL	1 2 3 4 5	38 18 27 13	38 18 21 8 0	23 3 3 1 0	7 2 1 0 0

categories as a function of dose and postexposure time. That mapping was done using Figs. 2 through 7 to construct the isoseverity contours shown in Figs. 16 through 22. First, the time points that correspond to discrete symptom severity levels were plotted along the midpoint lines of each dose range. The points were then connected by solid lines to form contours.

In Sec. 4, symptom categories were plotted as a function of time for each dose range. Transposition of those symptom severity levels to the time-dose plane is illustrated by Fig. 16. In that figure, UG symptom severity is shown. The horizontal axis shows time since exposure in hours. Days and weeks are also indicated. The axis extends to 1000 h (about six weeks), the time when the mainifest illness phase develops in the lowest dose range. The vertical axis shows prompt dose in rads (cGy). The horizontal lines correspond to the geometric midpoints of the dose ranges discussed in Secs. 3 and 4.

The typical course of radiation sickness is proceeded by a latency period. The sickness then begins with a brief and relatively intense prodromal phase followed by a remission phase which occurs before the full development of symptoms in the manifest illness phase. Figure 16 illustrates that progression. The contours for UG distress symptom severity reverse approximately 6 to 12 h after exposure, where the prodromal phase extends to the lowest dose level. The contours reverse again two to four days after exposure, where the remission phase extends to the highest dose level. The contours reverse a third time where the manifest illness phase is most pronounced, about four weeks after exposure for doses up to the range of 530 to 830 rads (cGy) range. The remission phase progressively disappears with increasing dose and is virtually nonexistent when doses reach the range of 1100 to 1500 rads (cGy).

The straight-line segments of those contours were plotted between points derived from Fig. 2, with connecting curves for the symptom severity contours in the reversal areas. Based on observation of the characteristics of the straight-line segments, the following

Table 3. Onseta and durationb of symptom complexes.

	3000-4500	۵																
	300	0			-		. ,	-=-	-									
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Dose B	530-830	0			64 75	210		9#	260	2						ć	235	
	530	۵			633		10	<u>~</u> ∞	7	j		16	23			6,	Σ T	
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	300	۵	1186	26 26 26	62													
	150-300	0	24 8	540	56													
	150	Ω																
	75-150	0																
	E S	Complex	112 111		113 111	113 121		-	1:4 113		124 111	124 121	124 141 124 151	•	134 112	134 121	_ •	71 - 24:

Time since exposure in hours, shown here as "C."

Duration as percent of time since exposure, shown here as "D."

Minority segment of survivor/fatality division

Disabled

Without early lower gastrointestinal distress

With early lower gastrointestinal distress

Onset^a and duration^b of symptom complexes (continued). Table 3.

Dose Bands (rads free-in-air)

4500	۵	30							28				
3000-4200	0	0.3							₹				
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830-1100	0	6.0	54 51	36	215	190 165	3	185	1.3	1. L		23	250
930	Ω	О п	1 9						th 3	56 10			
530-930	0	1.3	28						٦.۶	18 525			
230	۵	47	π9						36€	8 63			
300-530	0	1.9	22						2.8	3.8			
300	۵	36	50					1	۲, ۲	52			
150-300	o •	w,	<u>o</u>					:	12	. ar			
75-150	۵	200											
75-	0	Ŋ											
\$ 0 \$ 0 \$ 0	Symptom Complex		214 112 214 113	215 113						312 111 314 112 314 122			315 232 315 232 315 314

aTime since exposure in hours, shown here as "O."

buration as percent of time since exposure, shown here as "D."

c Minority segment of survivor/fatality division
d Disabled

e Without early lower gastrointestinal distress
f With early lower gastrointestinal distress

Onset⁸ and duration^b of symptom complexes (continued). Table 3.

Dose Bands (rads free-in-air)

200	Q		크 코 			
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1100-1	0		220	∄ . ←		
00	۵			33	57	د ت
830-1100	0			1.8 ±.5	14 340	340
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30	۵	11 23	22 ^e	14 32e 82	13	
300-530	0	3.1	r. #	(5.8 5 6.6	12	
00	۵		0	79		
150-300	0		6.1	6.7		
20	۵					
75-150	0					
	Symptom Complex	315 414 321 111 331 111 334 132 334 142	345 342 411 111 412 111	413 111 414 111	414 112 414 132 415 113 415 224 415 324	415 334 415 343 415 344 424 132 424 142

atime since exposure in hours, shown here as "0."
buration as percent of time since exposure, shown here as "D."
chinority segment of survivor/fatality division
disabled
ewithout early lower gastrointestinal distress
With early lower gastrointestinal distress

Onset^a and duration^b of symptom complexes (continued). Table 3.

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	200	۵	9	5 2	œ			7		,		0.	
	3000-4200	0	7.0	8.0	6.0			-		1.1	1.2	a .	
	900	۵	16	55	=			26		£. 4	10e	1.37e 19 16 153	
	1500-3000	0	275	بر - -	8.			8.		2.3	5.6	2.9 5.9 7 8.1	
	0051	۵		31		19 143		15 7e	17	70	•		
$\hat{\cdot}$	1100-1500	0		1.8		2.5		6.1 5.7	8.2	0.			
-in-air	100	۵		9		29 138	23 55						
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ands (re	330	۵	71	60 61 61									
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	530	۵	22										
	300-530	0	. ਜ										
	300	۵											
	150-300	0											
	150	۵											
	75-150	0											
		Symptom	ม32 111 นุช5 นุชุ3			515 111	515 112			515 224 515 311	515 321	515 331 515 332 515 333 515 334 515 431	

^aTime since exposure in hours, shown here as "0."

buration as percent of time since exposure, shown here as "D."

c Minority segment of survivor/fatality division
d bisabled

e Without early lower gastrointestinal distress
fwith early lower gastrointestinal distress

Onseta and durationb of symptom complexes (Concluded). Table 3.

	4500	Q	- 2	· •		. 1.						ζ.	-		
	3000-4500	0	2.5	5.1	5.7	6.7			. <u>.</u> .			ניז	4.5		
	3000	۵									83			22	
	1500-3000	0									3			230	
	1100-1500	Q						Ξ		9			ć	{ }	
٦	1100-	0						2.8		3.1				345	
e-in-ai	1100	Ω					-	6	0	68					
Dose Bands (rads free-in-air)	830-1100	0					2.7	5.3	0	3.2					
ands (r	830	۵					6		35	2					
Dose B	530-830	0					5.5		3.7	`					
	530	۵													
	300-530	0													
	300	Ω													
	150-300	0													
	75-150	۵													
	75-	0													
	10 40 E 3.0	Complex	515, 432 ^e	515 433 ^e	515 434	515 435 ^d	524 111		533 111					545 454 555 554 ^d	

15e 218e 12 12 13 318

aTime since exposure in hours, shown here as "0."
bDuration as percent of time since exposure, shown here as "D."
CMinority segment of survivor/fatality division
dDisabled
eWithout early lower gastrointestinal distress
With early lower gastrointestinal distress

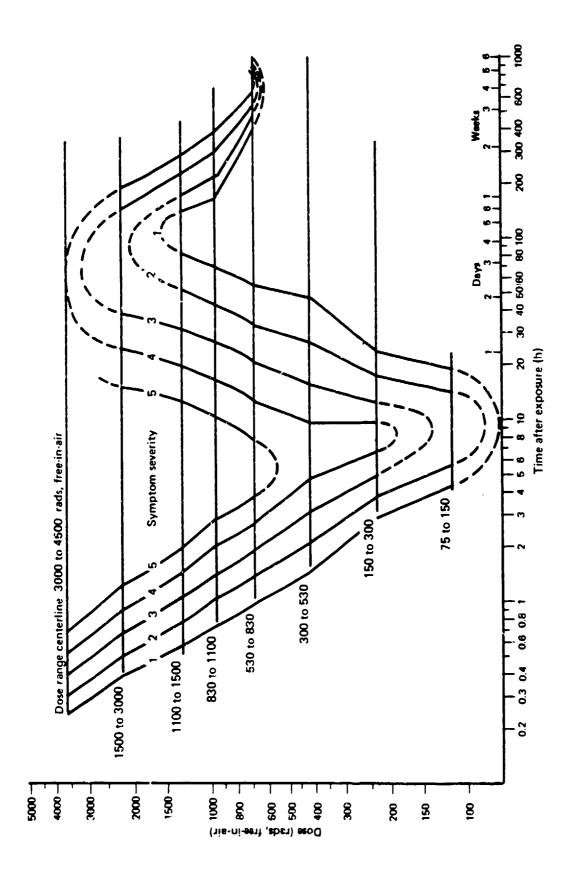


Figure 16. UG symptom severity.

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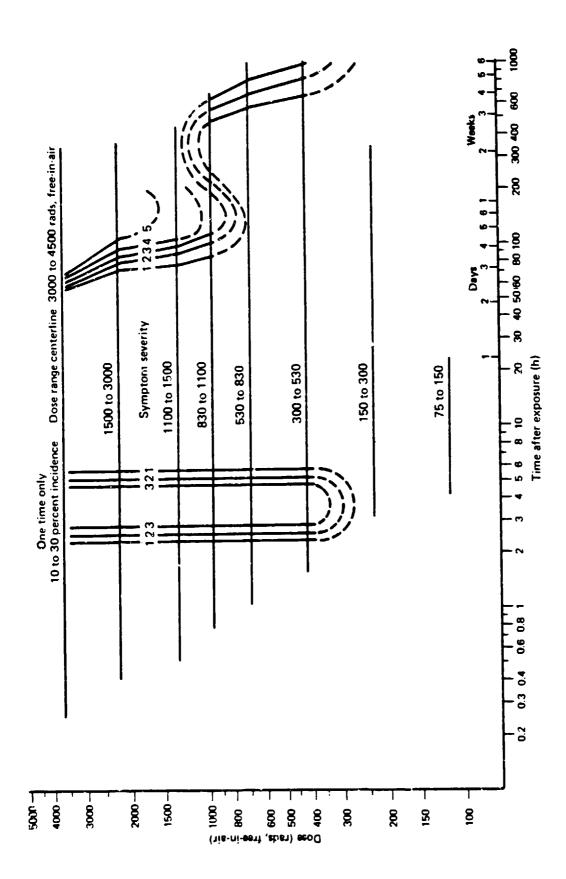


Figure 17. LG symptom severity.

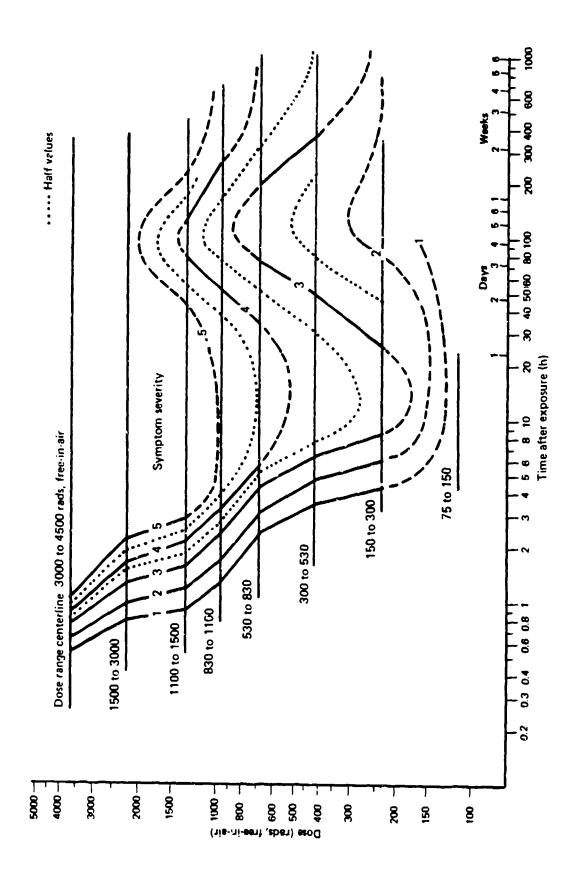


Figure 18. FW symptom severity.

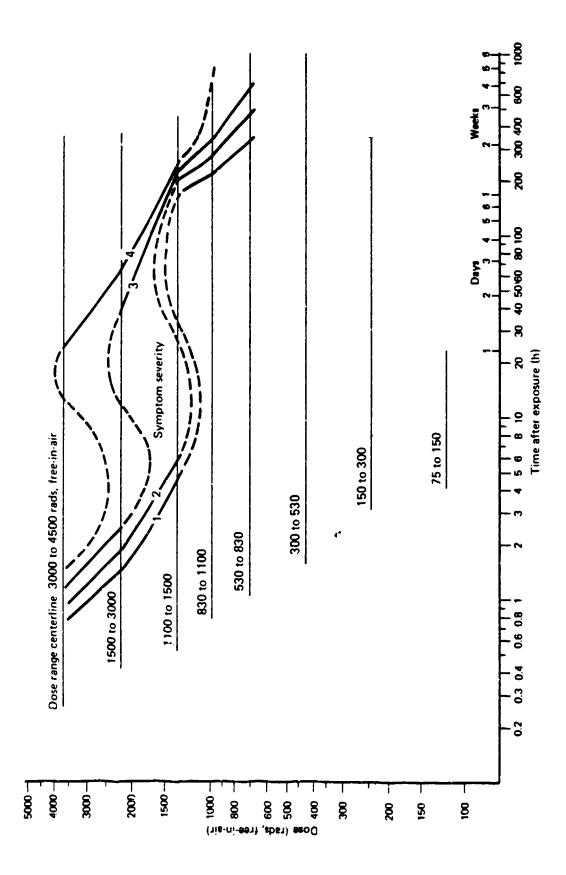


Figure 19. HY symptom severity.

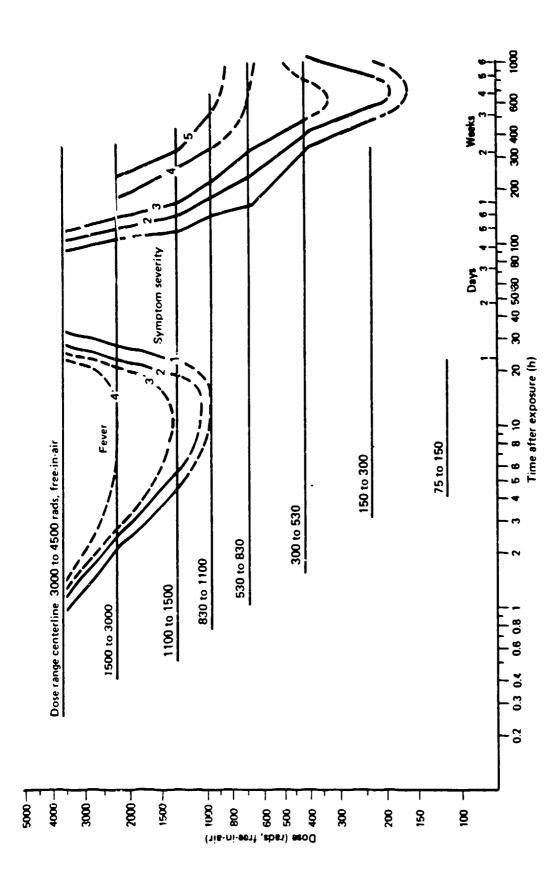


Figure 20. IB symptom severity.

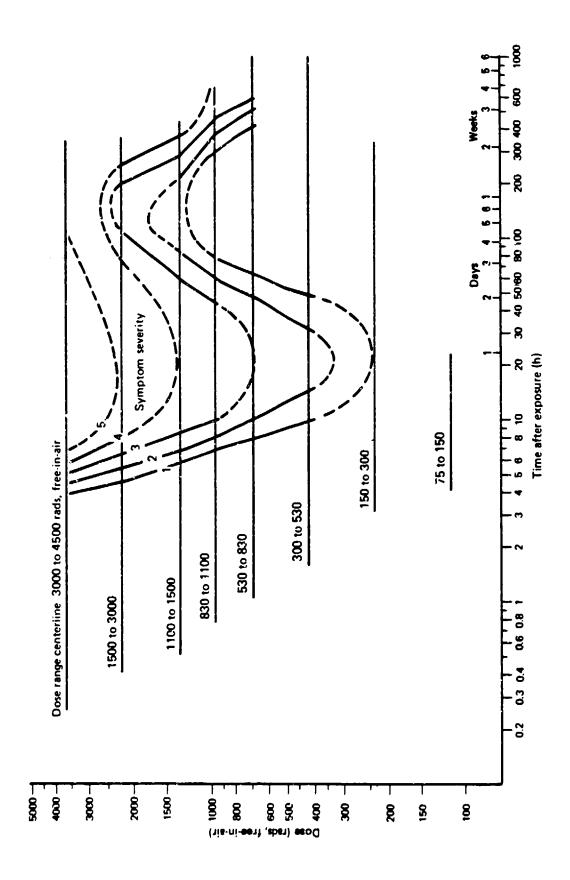


Figure 21. FL symptom severity.

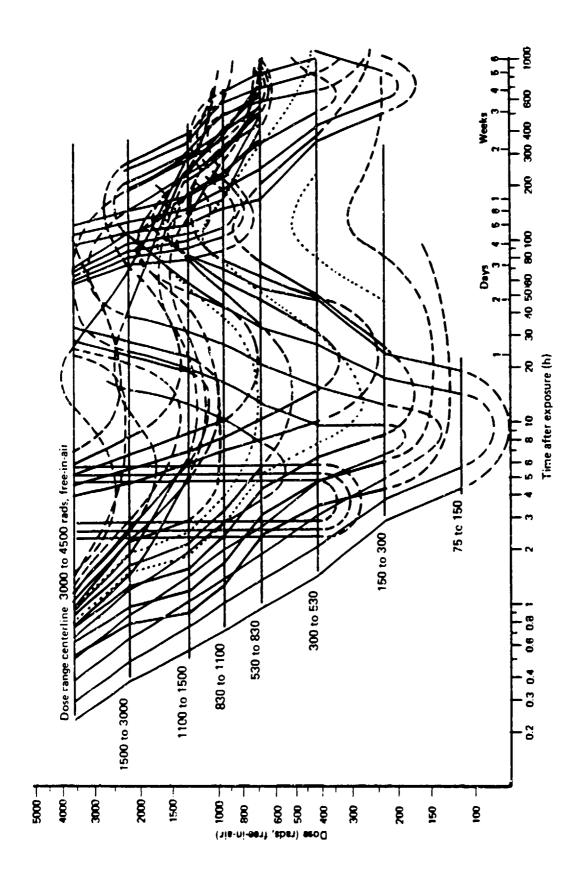


Figure 22. Six-dimensional map of symptom severity contours.

assumptions were formulated for sketching the connecting curves through the reversal areas.

First, Figs. 1 through 15 represent continuous quasianalog smoothing of the discrete symptom severity levels described in Sec. 2. Smoothing of the same data can be represented as symptom severity contour lines on a time-dose plane.

Second, the contour reversals cannot take the form of straight extensions of the straight-line segments plotted between established points. If the reversals were to be plotted as straight-line extensions, the contours would cross additional dose range centerlines which would not be consistent with the symptom severity profiles.

Third, although human response to radiation seems to be characteristically different depending on dose range, no discernable thresholds exist between dose ranges. On the contrary, the alignment of the severity level points plotted in Figs. 16 through 22 suggests that the phenomenon of human response to radiation severity, although it may involve such thresholds for the responses of individuals, constitutes a fairly smooth continuum of responses for an aggregated population.

Fourth, the isoseverity contours are continuous (as represented in Fig. 16), but that continuity is not explicitly defined by Baum et al. [1984] or Anno, Brode, and Washton-Brown [1982]. There is a lack of sufficient data to precisely shape the symptom severity contours at the point of lowest dose appearance in the prodromal phase, or at the point of highest dose appearance in the remission phase.

The following were used to develop a set of guidelines to make the connections between the isoseverity contour segments and to construct the curves.

• The segments connecting the symptom severity points in Figs. 8 through 15 are shown as straight lines, but curvature is implied. The complete contours are shown as curves in the combined plot of all the symptom complexes in Figs. 23 through 27.

the symptom complexes used on the Army questionnaire were the most representative complexes at the time the selections were made.

SECTION 6

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APPENDIX INCIDENCE OF SYMPTOMS

This appendix provides a graphical means of estimating the incidence of prodromal symptoms accompanying acute radiation sickness based on the symptomatology review by Baum et al. [1984] and data from Langham [1957], Lushbaugh [1982], Lushbaugh et al. [1969, 1973], and Withers [1982]. Incidence relationships as a function of dose are also given for selected symptom categories, based on both probit and logit forms assuming lognormal distributions of symptom incidence with dose.

UPPER GASTROINTESTINAL DISTRESS.

Estimated incidence for nausea (N) and vomiting (V) is given in Fig. 28 as a function of dose. The solid straight lines (N and V) were plotted on lognormal probability paper and are developed from data given by Langham [1957], Lushbaugh et al. [1969, 1973], and Lushbaugh [1982]. The alternating solid and dashed lines for nausea (N') and vomiting (V') for doses greater than 530 rads (cGy) correspond to those given by Baum et al. [1984] and assume that the incidence of those symptoms approach 100 percent at 830 rads (cGy). That suggests a higher incidence for UG symptoms than would be predicted by extrapolating the solid-line plots to higher equivalent doses. However, the fiducial limits given by the dotted and solid lines indicate the uncertainty in predicting incidence at high and low doses, as expected from probit analysis of less than ideal medical data.

FATIGABILITY AND WEAKNESS.

Estimated incidence for the FW category as a function of dose is given in Fig. 29. The solid straight line, FW(L) is developed from data given by Langham [1957], Lushbaugh et al. [1969, 1973], and Lushbaugh [1982]. The long dashed line FW(n), was developed from data given by Langham [1957] that assumes a normal distribution of incidence with dose based on probit analysis. At high dose [~ 800 rads

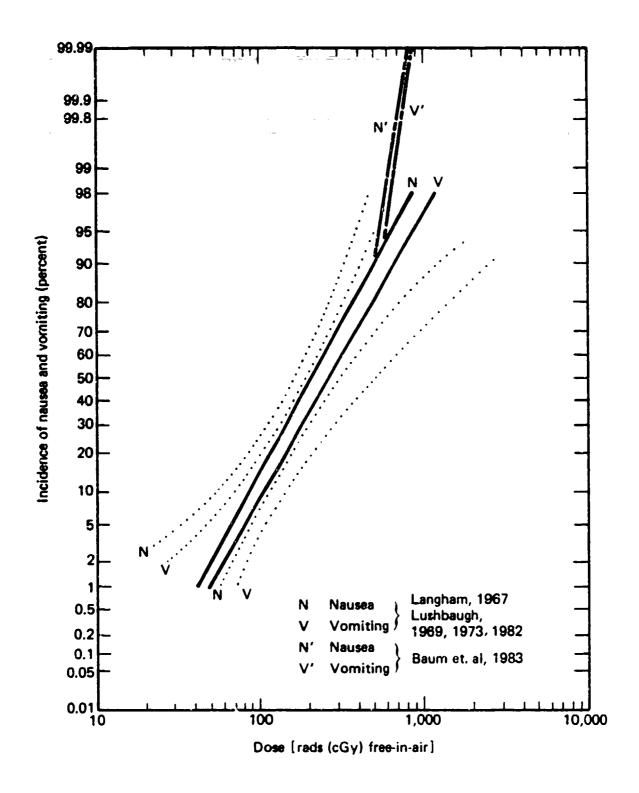


Figure 28. Incidence of UG.

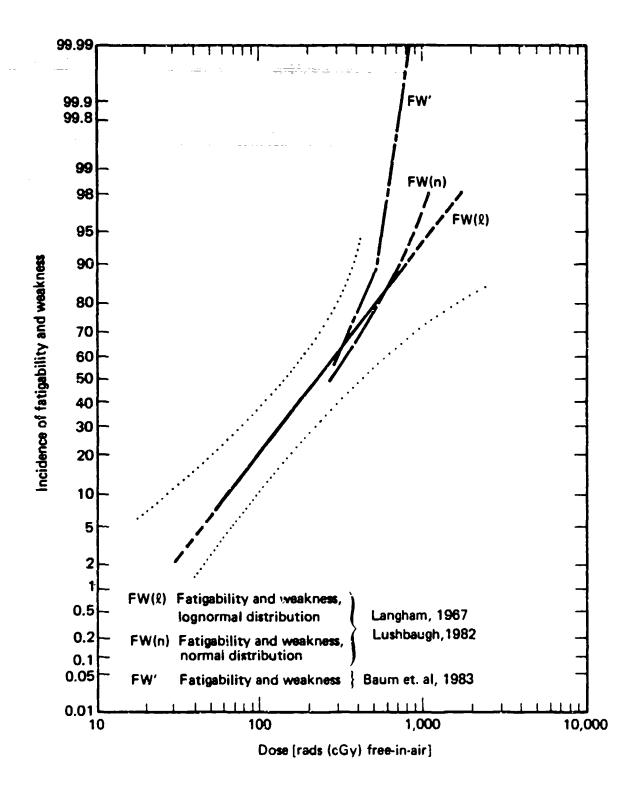


Figure 29. Incidence of FW.

(cGy)] and high incidence (~ 90 percent) the precision based on probit analysis is poor, assuming a lognormal distribution. On the other hand, at low dose [~ 70 rads (cGy)] and low incidence (~ 10 percent) the precision is poor, assuming a normal distribution.

The alternating solid and dashed line curve (FW') for doses greater than about 300 rads (cGy) corresponds to estimates given by Baum et al. [1984] that assume that the incidence of those symptoms approaches 100 percent at 830 rads (cGy). Again, that suggests a higher incidence for FW symptoms than would be predicted by extrapolating either plots (normal or lognormal) derived from probit analysis. The fiducial limits given by the dotted lines suggest a large measure of uncertainty regarding the incidence of FW symptoms, especially at high doses.

LOWER GASTROINTESTINAL DISTRESS.

The estimated incidence for LG symptoms is given in Fig. 30. The stepwise plot based on radiation therapy patient experience [Withers, 1982] is for early diarrhea (ED) occurring during the prodromal period which is different than the incidence of delayed diarrhea that occurs up to six weeks postexposure as given by the other curves.

The straight line D(1) is based on probit analysis [Lushbaugh et al., 1969] assuming a lognormal distribution of incidence and the curved line D(n) is based on normal distribution of incidence [Langham, 1957]. For the lognormal assumption, the precision based on probit analysis of data is poor at the high dose end of the curve. The alternating solid and dashed line curve D', for doses greater than about 300 rads (cGy) corresponds to estimates based on the review by Baum et al. [1984], which indicates the incidence of those symptoms approach 100 percent for doses over 830 rads (cGy). Baum et al. [1984] point out that doses from about 1050 to 1500 rads (cGy) result in depletion of the epithelial intestinal lining extensive enough to result in death from septicemia within 2 to 3 weeks. The extent of

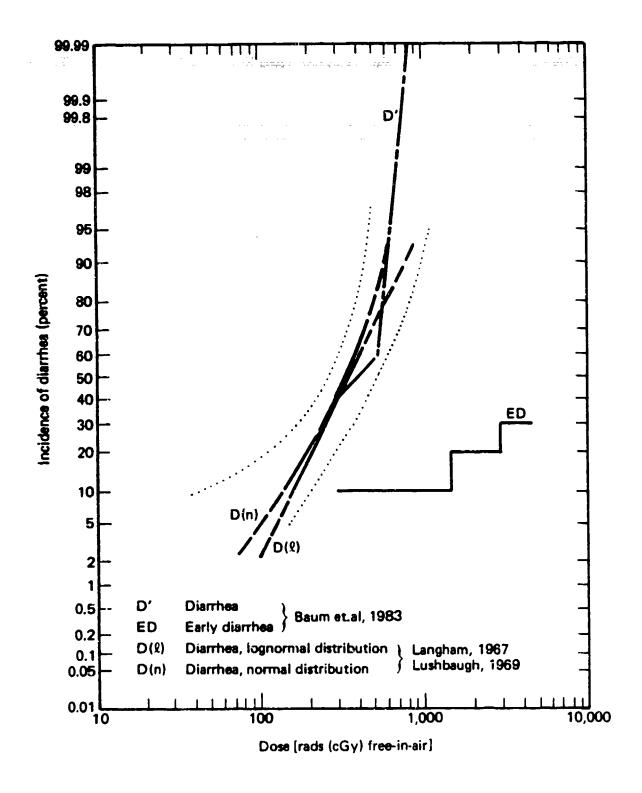


Figure 30. Incidence of LG.

gut damage is expected to cause severe diarrhea episodes in essentially all exposed individuals.

PRODROMAL SYMPTOMS.

Incidence of prodromal symptom categories is plotted in Fig. 31. In review of the symptomatology of acute radiation sickness, Baum et al. [1984] were not able to identify any specific research that applied rigorous statistical methods to existing data to determine symptom incidence correlation in exposed individuals. The lack of appropriate medical data have hampered such efforts. Consequently, the precise extent to which some or all symptoms of acute radiation sickness occur and over what dose levels and postexposure times is not explicitly known for large populations where there is a variation in individual sensitivity.

The overwhelming assertion among investigators who have studied acute ionizing radiation effects in humans is that if symptoms occur at all, nearly all are expressed to some degree, particularly with increasing dose beyond the 100 to 200 rads (cGy) level. The conservative approach presumes the presence of some form of acute radiation sickness with dose based on the left-most envelope of symptom incidence curves listed in Fig. 31. That is, although Fig. 31 suggests that FW may occur more frequently than nausea and vomiting up to doses of about 170 rads (cGy), the latter may or may not occur jointly with FW. For doses from about 170 to 530 rads (cGy), Fig. 31 indicates that nausea occurs somewhat more frequently than the other symptoms. For doses greater than 530 rads (cGy), Fig. 31 suggests that prodromal symptoms all rapidly increase to similar high incidences with dose. For completeness, the FW plot, assuming a normal distribution of incidence (from Fig. 29) and the incidence of ED (from Fig. 30) are also shown in Fig. 31.

Functional relationships have been developed for the envelope symptoms, N, V, N', and $FW(\mathfrak{k})$ given in Fig. 31, which can be used to compute incidence. Those relationships assume a lognormal distribution of incidence with dose f(D), given as

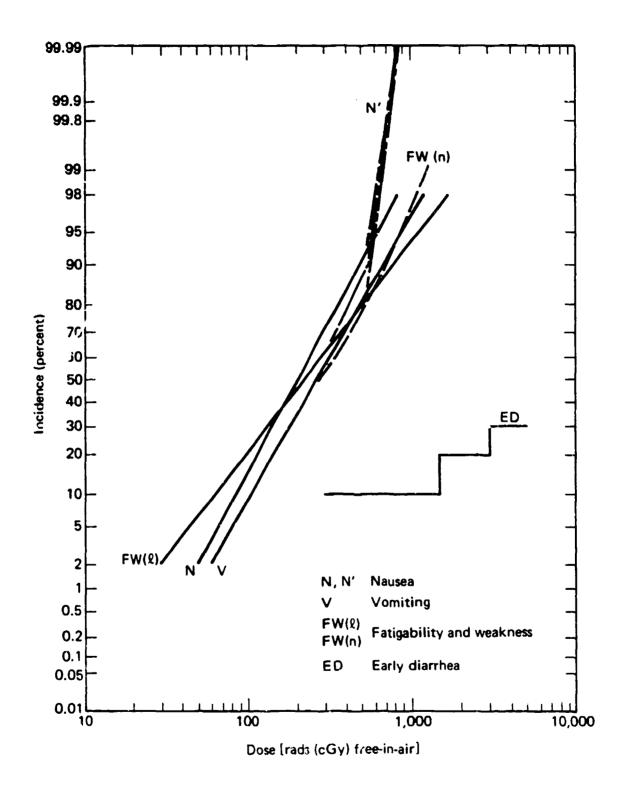


Figure 31. Incidence of prodromal symptoms.

$$f(D) = \frac{1}{\sqrt{2\pi}\sigma D} \left[\exp \left(-\frac{\ln D - \mu}{\sigma}\right)^2 \right] , \qquad (1)$$

where mean, $\mu = E[ln(D)]$,

variance, $\sigma^2 = var[ln(D)]$.

The mean, variance, and median of the dose are given as

mean,
$$\overline{D} = E(D) = e^{(\mu + \sigma^2/2)}$$
,

median, $M = e^{\mu}$,

variance,
$$S^2 = var(D) = e^{(2\mu + \sigma^2)} (e^{\sigma^2} - 1)$$
.

The relationship for symptom incidence with dose is then

$$I(D) = \int_{0}^{D} f(D^{\dagger}) dD^{\dagger}$$
, (2)

which is not integratable in closed form. However, making the transformation $x = (\ln D - \mu)/\sigma$ in Eq. (1), Eq. (2) may be rewritten as

$$I(x) = \frac{1}{\sqrt{2\pi}} \int_{-\pi}^{x} e^{-(1/2) x^{2}} dx' , \qquad (3)$$

which is the cumulative unit normal. Then, since

$$\frac{2}{\sqrt{\pi}} \int_{-\infty}^{2} e^{-iz^{2}} dz' = erf(z)$$
,

the incidence I(D) may be given by

$$I(D) = \frac{1}{2} \left[1 + \operatorname{erf} \left(\frac{\ln D - \mu}{\sqrt{2\sigma}} \right) \right] . \tag{4}$$

Parameter values for Eq. (4) are given in Table 4 to compute the incidence of the envelope symptoms in Fig. 31.

A simpler relationship based on the logistic function given by Finney [1964] may also be employed to compute incidence as a function dose which closely approximates the cumulative lognormal given by Eq. (4).

$$I(D) = \frac{1}{1 + \exp[-(\alpha + \beta \ln D)]}, \qquad (5)$$

where, α and β are fit parameters whose values are also given in Table 4 for the envelope symptoms in Fig. 31. The parameter values given below are obtained by matching slopes and requiring the equivalency conditions, I(D) = 0.5,

matching slopes for
$$\beta = \frac{4}{\sigma\sqrt{2\pi}}$$
,

equivalency condition $\mu = \alpha/\beta$.

Figure 32 compares symptom incidence relationships with dose as computed by both Eq. (4) (solid curves) and Eq. (5) (dashed curves). Given the uncertainty in the symptom incidence relationships, the logistic function given by Eq. (5) is appropriate for computing symptom incidence.

Although Eqs. (4) and (5) or Fig. 31 could be used to estimate symptom incidence over the whole range of dose, again, we point out that selected portions of the relationships can be employed (i.e., based on dose considerations) to develop a symptom envelope depending upon the focus of interest. For example, if FW is the most important debilitating consideration compared with nausea, then the FW rather than the UG symptom category could be chosen to form the symptom incidence envelope.

POSSOCIONE DE PROPERTOR

Table 4. Prodromal symptom incidence relationship parameters.

		Logn	Lognormal ^a			Log 1	Logistic
Symptom	a	0	þa	Σ	တ	ð	30.
Nausea (N)	5.3337	0.69521	263.8	263.8 207.2	208.0	-12.2429	2,29538
Nausea (N')	6.0147	0.19290	417.1	14.604	81.21	81.21 -49.7567	8.27252
Vomiting (V)	5.6195	0.71598	356.3	356.3 275.8	291.6	291.6 -12.5247	2.22879
Fatigability and weakness [FW(£)]	5.3821	0.98115	351.9	217.5	447.7	351.9 217.5 447.7 - 8.7536	1.62643

a Lognormal distribution parameters are as follows:

$$\mu = E(\ln D)$$
 $\overline{D} = E(D) = \exp(\mu + 1/2 o^2)$.

 $o = \left[\operatorname{var}(\ln D) \right]^{1/2}$ $M = \exp(\mu)$
 $S = \left[\operatorname{var}(D) \right]^{1/2} = \left\{ \left[\exp(2\mu + o^2) \right] \left[\exp(o^2) - 1 \right] \right\}^{1/2}$

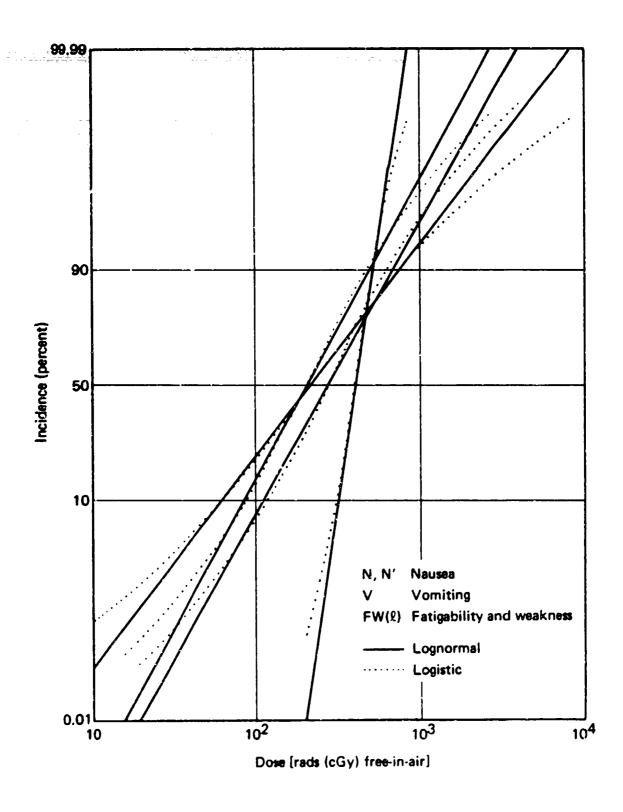


Figure 32. Incidence of prodromal symptoms—lognormal and logistic relationships.

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ATTN: COMMANDER

USS LONG BEACH (CGNQ)

ATTN: COMMANDING OFFICER

DEPARTMENT OF THE AIR FORCE

AERONAUTICAL SYSTEMS DIVISION, AFSC

ATTN: XRO/MAF

AF/INE

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ATTN: INA

AFIS/INT

ATTN: INT

AIR FORCE LOGISTICS COMMAND

ATTN: SECURITY POLICE

AIR FORCE OFFICE OF SECURITY POLICE

2 CYS ATTN: AFOSP/SPPC

AIR FORCE SYSTEMS COMMAND

ATTN: DL

ATTN: SD

ATTN: SECURITY POLICE

ATTN: XR

AIR FORCE WEAPONS LABORATORY, AFSC

ATTN: SUL

AIR UNIVERSITY

ATTN: AU/SP

ATTN: STRATEGIC STUDIES

AIR UNIVERSITY LIBRARY

ATTN: AUL-LSE

ATTN: LIBRARY

ASSISTANT CHIEF OF THE AIR FORCE

ATTN: SAF/ALR

DEPUTY CHIEF OF STAFF/AF-RDQI

ATTN: AF/RDOI

DEPUTY CHIEF OF STAFF/X00

ATTN: AF/XOC

DEPUTY CHIEF OF STAFF/XOX

ATTN: AFXOXFM PLNS FRC DEV MUN PLNS

ATTN: AFXOXFS FRC DEV STRAT OFF FRC

ELECTRONIC SYSTEMS DIVISON/OCB

3 CYS ATTN: OCB

SPACE COMMAND

ATTN: SECURITY POLICE

SPACE DIVISION/YH

ATTN: YH (DSCS III)

STRATEGIC AIR COMMAND

ATTN: SECURITY POLICE

STRATEGIC AIR COMMAND/NRI-STINFO

ATTN: NRI/STINFO

STRATEGIC AIR COMMAND/SPD

ATTN: SPD

STRATEGIC AIR COMMAND/STIC

ATTN: STIC

STRATEGIC AIR COMMAND/XPQ

ATTN: XPO

STRATEGIC AIR COMMAND/XPX

ATTN: XPZ

TACTICAL AIR COMMAND TAC/DOA

ATTN: TAC/DOA

TACTICAL AIR COMMAND/XPJ

ATTN: TAC/XPJ

U S AIR FORCE IN EUROPE/SP

2 CYS ATTN: USAFE/SPO

DEPARTMENT OF THE AIR FORCE (CONTINUED)

U S AIR FORCES IN EUROPE/DEX ATTN: USAFE/DEXX

U S AIR FORCES IN EUROPE/DOT ATTN: USAFE/DOQ

U S AIR FORCES IN EUROPE/INAT ATTN: USAFE/INAT

USAF SPECIAL OPERATIONS SCHOOL ATTN: COMMANDANT CC

1ST ACCS

ATTN: DOF

2ND ACCS

ATTN: DOC

3280TH TECH TRAINING SQ ATTN: TG1CC

DEPARTMENT OF ENERGY

DEPARTMENT OF ENERGY ATTN: D RICHMOND

DEPARTMENT OF ENERGY ATTN: OMA, DP-22

DEPARTMENT OF ENERGY

ATTN: OFFICE OF INTELLIGENCE

ATTN: OMA, DP-22

ATTN: SAFEGUARDS & SECURITY ATTN: TECH & INTELLIGENCE DIR

UNIVERSITY OF CALIFORNIA LAWRENCE LIVERMORE NATIONAL LAB

ATTN: L-35

ATTN: L-38

ATTN: L-389

ATTN: L-450 W HOGAN

ATTN: L-53 TECH INFO DEPT LIB ATTN: M GUSTAVSON D DIVISION

ATTN: Z DIVISION LIBRARY

LOS ALAMOS NATIONAL LABORATORY

ATTN: F601 T DOWLER
ATTN: REPORT LIBRARY

ATTN: R SANDOVAL

SANDIA NATIONAL LABORATORIES

ATTN: TECH LIB 3141 RPTS RCVG CLRK

ATTN: 0333 R B STRATTON

OTHER GOVERNMENT

BUREAU OF ALCHOL TABACCO & FIREARMS
ATTN: CHIEF SPECIAL OPNS DIV

BUREAU OF POLITICO MILITARY AFFAIRS
ATTN: PM/STM

CENTRAL INTELLIGENCE AGENCY

ATTN: COUNTER-TERRORIST GP

ATTN: DIRECTOR OF SECURITY

ATTN: MEDICAL SERVICES

ATTN: NIO-T

ATTN: N10 - STRATEGIC SYS

ATTN: OFFICE OF GLOBAL ISSUES

ATTN: R & D SUBCOMMITTEE

ATTN: SECURITY COMMITTEE

ATTN: TECH LIBRARY

COMMITTEE ON ARMED SERVICES

ATTN: STAFF DIR & CHIEF COUNSEL

DOT/FEDERAL AVIATION ADMINISTRATION
ATTN: DIR OF CIVIL AVIATION SEC

FEDERAL BUREAU OF INVEST ACADEMY
ATTN: BEHAVIORAL RSCH UNIT

2 CYS ATTN: LIBRARY

FEDERAL BUREAU OF INVESTIGATION
3 CYS ATTN: TERRORIST RSCH & ANALYTICAL CTR

FEDERAL EMERGENCY MANAGEMENT AGENCY

ATTN: CIVIL SECURITY DIVISION

ATTN: G ORRELL NP-CP

ATTN: OFC OF RSCH/NP H TOVEY

GENERAL SVCS ADMINISTRATION

ATTN: PS

HOUSE PERM SELECT COMMITT ON INTELL

ATTN: STAFF DIRECTOR

INTERPOL US NATL CENTRAL BUREAU

ATTN: CHIEF

METRO TRANSIT POLICE

ATTN: CHIEF

NATIONAL BUREAU CF STANDARDS

ATTN: LAW ENFORCEMENT

NATIONAL BUREAU OF STANDARDS

ATTN: TECH A219

NATL CRIMINAL JUSTICE REFERENCE SVC

2 CYS ATTN: D GALARRAGA

SELECT COMMITTEE ON INTELLIGENCE

ATTN: STAFF DIRECTOR

SUBCOMMITTEE ON SEC & TERRORISM

ATTN: CHIEF COUNSEL/STAFF DIR

OTHER GOVERNMENT (CONTINUED)

U S CAPITOL POLICE ATTN: CHIEF

U S COAST GUARD
ATTN: PORT & ENVIR SAFETY

U S COAST GUARD ACADEMY ATTN: LIBRARY

U S DEPARTMETN OF STATE
ATTN: A/SY/CC/TAG
ATTN: A/SY/DASS
ATTN: A/SY/OP/T
ATTN: FAIM/LR

2 CYS ATTN: M/CTP ATTN: M/MED

U S NUCLEAR REGULATORY COMMISSION
ATTN: DIR DIV OF SAFEGUARDS
ATTN: OFC OF INSP & ENFORCEMENT

DEPARTMENT OF DEFENSE CONTRACTORS

ADVANCED RESEARCH & APPLICATIONS CORP ATTN: DOCUMENT CONTROL

BDM CORP

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BOEING CO

ATTN: D CHOATE ATTN: J W RUSSELL

COMPUTER SCIENCES CORP ATTN: F EISENBARTH

GRUMMAN-CTEC, INC ATTN: S SHRIER

HORIZONS TECHNOLOGY, INC ATTN: J PALMER

IIT RESEARCH INSTITUTE
ATTN: DOCUMENTS LIBRARY

INSTITUTE FOR DEFENSE ANALYSE'S
ATTN: CLASSIFIED LIBRARY
ATTN: J GROTE

JAYCOR

ATTN: R SULLIVAN

KAMAN SCIENCES CORP ATTN: F SHELTON

KAMAN SCIENCES CORP ATTN: E CONRAD KAMAN TEMPO

ATTN: DASIAC

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ATTN: DASIAC

MARTIN MARIETTA DENVER AEROSPACE ATTN: J DONATHAN

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PACIFIC-SIERRA RESEARCH CORP
2 CYS ATTN: D WILSON
5 CYS ATTN: G ANNO
ATTN: H BRODE, CHAIRMAN SAGE
2 CYS ATTN: S BAUM

PACIFIC-SIERRA RESEARCH CORP ATTN: D GORMLEY

ATTN: G MCCLELLAN

R & D ASSOCIATES ATTN: C K B LEE

ATTN: C KNOWLES ATTN: D SIMONS

2 CYS ATTN: DOCUMENT CONTROL

ATTN: F A FIELD

R & D ASSOCIATES
ATTN: A DEVERILL
ATTN: J THOMPSON

RAND CORP

ATTN: P DAVIS ATTN: V JACKSON

RAND CORP

ATTN: B BENNETT

ROCKWELL INTERNATIONAL CORP ATTN: J HOWE

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ATTN: J MARTIN ATTN: J WARNER ATTN: M DRAKE ATTN: R J BEYSTER

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ATTN: J PETERS ATTN: J SHANNON ATTN: L GOURE ATTN: M FINEPER ATTN: W LAYSON

DEPT OF DEFENSE CONTRACTORS (CONTINUED)

SCIENCE APPLICATIONS INTL CORP
ATTN: D KAUL

TRW ELECTRONICS & DEFENSE SECTOR
ATTN: D SCALLY
ATTN: N LIPNER
ATTN: R BURNETT ATTN: D KAUL

SCIENCE APPLICATIONS INTL CORP ATTN: R CRAVER

ATTN: R BURNETT

TRW ELECTRONICS & DEFENSE SECTOR ATTN: P DAI